

# Macular and Peripapillary Microvasculature in Acromegaly, an Optical Coherence Tomography Angiography Study: Cross-Sectional Study

## Akromegalide Makular ve Peripapiller Mikrovasküler Yapı, Optik Koherens Tomografi Anjiyografi Çalışması: Kesitsel Çalışma

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**ABSTRACT Objective:** To assess macular and optic nerve head capillary network in patients with acromegaly using optical coherence tomography angiography (OCTA). **Material and Methods:** This study included 54 acromegaly patients and 50 healthy control subjects. All participants underwent comprehensive ophthalmological examinations, including optical coherence tomography and OCTA. Vessel densities (VD) in the superficial (SCP) and deep capillary plexuses (DCP), and the radial peripapillary capillary (RPC) segment were recorded. **Results:** The corrected distance visual acuity was significantly worse in the acromegaly group. Both superior and nasal retinal nerve fiber layer (RNFL) thicknesses were significantly thinner, in patient group ( $p<0.05$ ). Optic neuropathy (ON) was detected in 40.7% of patients. RPC VD was significantly reduced in the inferior region ( $p=0.034$ ), and macular OCTA analysis showed decreased VD in SCP whole, inferior, nasal, and DCP inferior and nasal quadrants in the acromegaly group. In patients with ON, RNFL superior thickness showed a negative correlation with RPC superior VD ( $r=-0.475$ ,  $p=0.026$ ). Correlations were observed between RNFL temporal thickness and RPC temporal VD ( $r=0.584$ ,  $p=0.004$ ) and between RNFL nasal thickness and RPC nasal VD ( $r=0.510$ ,  $p=0.015$ ). In the group without ON, RNFL nasal thickness negatively correlated with RPC nasal VD ( $r=-0.478$ ,  $p=0.006$ ). **Conclusion:** Our study showed significantly reduced VD in the RPC inferior quadrant and various macular SCP and DCP quadrants in acromegaly patients. Our findings suggest that vascular compensatory mechanisms may activate prior to ON and might persist even with ON. OCTA provides a noninvasive means to explore retinal microcirculation.

**ÖZET Amaç:** Akromegali hastalarında, optik koherens tomografi anjiyografi (OKTA) ile makular ve optik sinir başı kapiller damar yoğunluğunu (DY) değerlendirilmesi amaçlandı. **Gereç ve Yöntemler:** Bu kesitsel çalışmaya, 54 akromegali hastası ve 50 sağlıklı katılımcı dâhil edildi. Tüm katılımcılara kapsamlı göz muayeneleri yapıldı, OKT ve OKTA görüntülemeleri gerçekleştirildi. Süperfisyal kapiller pleksus (SKP) ve derin kapiller pleksus (DKP) ve radial peripapiller kapiller (RPK) segmentlerinde DY'ler kaydedildi. **Bulgular:** Akromegali grubunda en iyi düzeltilmiş görme keskinliği anlamlı derecede düşük, superior ve nasal retinal sinir lifi tabaka [retinal nerve fiber (RNFL)] kalınlıkları anlamlı derecede incedi ( $p<0,05$ ). Optik nöropati (ON) %40,7 oranında hastada tespit edildi. RPK DY, inferior bölgede anlamlı azalmıştı ( $p=0,034$ ). Akromegali grubunda SKP bütün, inferior, nazal ve DKP inferior ve nazal bölgelerde DY'nin kontrole göre azaldığı gözlemlendi. ON bulunan hastalarda superior RNFL kalınlığı ile RPK superior DY arasında negatif korelasyon ( $r=-0,475$ ,  $p=0,026$ ) bulundu. Temporal RNFL kalınlığı ile RPK temporal DY ( $r=0,584$ ,  $p=0,004$ ) ve nazal RNFL kalınlığı ile RPK nazal DY ( $r=0,510$ ,  $p=0,015$ ) arasında pozitif korelasyon gözlemlendi. ON bulunmayan grupta ise nazal RNFL kalınlığı ile RPK nazal VD arasında negatif korelasyon ( $r=-0,478$ ,  $p=0,006$ ) saptandı. **Sonuç:** Çalışmamızda, akromegali hastalarında RPK inferior ve çeşitli SKP ve DKP alt bölgelerinde anlamlı DY azalması gözlemlenmiştir. Çalışmamız sonuçları, vasküler kompensasyon mekanizmalarının ON gelişiminden önce aktive olabildiğini ve ON mevcut olduğunda bile devam edebileceğini öne sürmektedir. OKTA, retinal mikro dolaşımın noninvaziv bir şekilde incelenmesini sağlayarak akromegali hastalarındaki erken mikrovasküler değişikliklerin anlaşılmasına yardımcı olabilir.

**Keywords:** Acromegaly; insulin like growth factor-1; optical coherence tomography angiography; ocular hypoperfusion; vessel density

**Anahtar Kelimeler:** Akromegali; insülin benzeri büyüme faktörü-1; optik koherens tomografi anjiyografi; oküler hipoperfüzyon; damar yoğunluğu

**TO CITE THIS ARTICLE:**

Çiloğlu Hayat Ş, Yılmaz YC, Kelebek M, Hatipoğlu E. Macular and peripapillary microvasculature in acromegaly, an optical coherence tomography angiography study: Cross-sectional study. Türkiye Klinikleri J Ophthalmol. 2025;34(1):17-23.

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Peer review under responsibility of Türkiye Klinikleri Journal of Ophthalmology.

**Received:** 22 Jul 2024

**Received in revised form:** 02 Sep 2024

**Accepted:** 16 Nov 2024

**Available online:** 03 Jan 2025

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Acromegaly is a rare disease that occurs secondary to high levels of growth hormone (GH) and insulin like growth factor-1 (IGF-1). The most common cause is pituitary adenoma (PA), in some rare cases, an ectopic focus may produce the GH.<sup>1,2</sup> The clinical manifestations of acromegaly encompass a wide spectrum of symptoms, ranging from soft tissue swelling, to arterial hypertension, diabetes mellitus, and heart failure.<sup>3</sup> In ocular tissues, acromegaly can lead to changes in visual acuity (VA), visual field (VF) defects, and thinning of the retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) due to the compressive effect of the adenoma, as well as alterations in corneal and retinal thickness and intraocular pressure (IOP).<sup>4,5</sup>

While the ocular manifestations of acromegaly have been extensively studied, comprehensive evaluations of macular and peripapillary perfusion are limited.<sup>6-9</sup> This study aims to address the gap by investigating the capillary networks in both the macula and optic nerve head of patients with acromegaly, using optical coherence tomography angiography (OCTA) for comprehensive assessment.

## MATERIAL AND METHODS

This study was conducted retrospectively. Ethics approval for this study was obtained from the Ethics Committee of Başakşehir Çam and Sakura City Hospital, Health Sciences University, İstanbul (date: June 26, 2024, no: 2024-20). The study protocol followed the rules of Helsinki Declaration.

The files of patients diagnosed with acromegaly and followed up by the endocrinology department, who were also consulted for possible ocular implications at the ophthalmology clinic between February 2022 and February 2024, were reviewed. Eligibility criteria included a confirmed diagnosis of acromegaly, established through comprehensive examinations, blood tests conducted by an endocrinologist, and magnetic resonance imaging indicating the presence of a PA. The serum IGF-1 levels, tumor diameters, and disease durations of acromegaly patients were recorded. A group of healthy subjects composed of volunteers from our clinics. Only the right eyes of the participants were included in the study. Exclusion cri-

teria comprised individuals with any other central nervous system diseases, the presence of ocular abnormalities that could lead to visual impairment or optic nerve diseases other than PA, patients whose IGF-1 serum levels couldn't be detected in the files, refractive disorders exceeding  $\pm 2$  diopters of myopia or hypermetropia, and systemic conditions like diabetes mellitus and hypertension that could affect visual function or induce vascular changes. Additionally, patients with suboptimal quality optical coherence tomography (OCT) and OCTA images were excluded.

Ophthalmological examinations were conducted by a single ophthalmologist (S.C.H.). The examinations included assessments of corrected distance visual acuity (CDVA), color vision, IOP, and fundus examination, followed by standard automated perimetry, OCT, and OCTA. Optic neuropathy (ON) was defined based on the ophthalmological examination, including CDVA, color discrimination, and optic nerve head examination, VF test, and RNFL thickness. Macular and RNFL thickness and OCTA imaging were performed using Topcon DRI OCT Triton Swept Source-OCT (Topcon Corporation, Tokyo, Japan). OCT images in a raster pattern covering a  $6 \times 6$  mm area of the disc and a  $7 \times 7$  mm area of the macula, were obtained. Only measurements with proper centering and accurate segmentation were included. Motion and projection artifacts were minimized using the built-in eye-tracking system and artifact removal algorithm during imaging. The OCTA scans the macular area centered on the fovea, covering a  $6 \times 6$  mm field with each scan consisting of 320 B-scan clusters. The automated layer segmentation provided by the equipment's software (IMAGENet 6, Topcon Corporation, Japan; version 1.21.11783) produced various en face slabs. Vessel density (VD) was measured, including superficial retinal capillary plexus (SCP) and deep retinal capillary plexus (DCP). In the macular region, SCP en face images were obtained from a slab extending from  $2.6 \mu\text{m}$  below the ILM to  $15.6 \mu\text{m}$  beneath the interface between the inner plexiform layer (IPL) and inner nuclear layer (INL). DCP images were acquired from  $15.6 \mu\text{m}$  to  $70.2 \mu\text{m}$  below the IPL/INL interface. The peripapillary OCTA scan is performed using volumetric scans cover an area of  $4.5 \times 4.5$  mm

centered around the optic disc. The radial peripapillary capillary (RPC) segment extended from the ILM to the posterior boundary of the RNFL.

Statistical analysis was carried out using the SPSS 25.0 (IBM, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to examine the data distribution. Descriptive data were summarized with mean and standard deviation or median and range (minimum–maximum). The Spearman’s rho test was used to perform correlation analysis. The Mann-Whitney U test was used for intergroup comparisons, based on the non-normal distribution of the data. A significance level of  $p < 0.05$  was considered statistically significant.

## RESULTS

The study comprised 54 eyes from 54 patients diagnosed with acromegaly and 50 eyes from 50 healthy control subjects. In the acromegaly group, there were 27 females and 27 males, while the control had 26 females and 24 males, with no significant difference between the groups ( $p > 0.05$ ). The median age was 45 (23–66) years in the acromegaly group and 43 (29–75) years in the control group ( $p = 0.063$ ). In the acromegaly group, the median level of IGF-1 was 401 (54–1523) ng/mL, and the median follow-up period after diagnosis was 4 (1–14) years.

The CDVA was significantly worse in the acromegaly group compared to the control group ( $0.14 \pm 0.5$  vs  $0.0 \pm 0.0$  LogMAR) ( $p < 0.001$ ). It was observed that the superior and nasal RNFL were significantly thinner in the acromegaly group than the control group (Table 1).

RPC VD was found to be significantly reduced in the inferior region in the acromegaly group (Table

**TABLE 1:** Comparison of optical coherence tomography parameters between groups.

Thickness of regions ( $\mu\text{m}$ )	Acromegaly	Control	p value
	group	group	
Central Macula	264.41 $\pm$ 45.02	265.16 $\pm$ 13.857	0.902
RNFL Superior	127.19 $\pm$ 19.2	134.74 $\pm$ 17.2	<b>0.044</b>
RNFL Temporal	73.39 $\pm$ 10.1	75.66 $\pm$ 9.646	0.167
RNFL Inferior	138.52 $\pm$ 19.7	136.24 $\pm$ 11.250	0.175
RNFL Nasal	75.41 $\pm$ 9.2	85.94 $\pm$ 8.363	<b>&lt;0.000</b>

RNFL: Retinal nerve fiber layer; Mann-Whitney U test.

**TABLE 2:** The mean radial peripapillary capillary vessel density of each groups.

Vessel density (%)	Acromegaly	Control	p value
RPC Superior	54.49 $\pm$ 3.0	55.44 $\pm$ 1.3	0.079
RPC Temporal	52.78 $\pm$ 3.3	52.16 $\pm$ 3.0	0.486
RPC Inferior	52.98 $\pm$ 3.3	54.3 $\pm$ 2.9	<b>0.034</b>
RPC Nasal	51.60 $\pm$ 3.5	52.78 $\pm$ 2.5	0.091

RPC: Radial peripapillary capillary; Mann-Whitney U test.

**TABLE 3:** The mean macular OCTA results for each groups.

Vessel density (%)	Acromegaly	Control	p value
<b>SCP Whole</b>	19.87 $\pm$ 3.6	23.87 $\pm$ 3.0	<b>&lt;0.000</b>
SCP Superior	46.09 $\pm$ 3.4	46.06 $\pm$ 3.1	0.881
SCP Temporal	46.51 $\pm$ 3.0	46.73 $\pm$ 3.0	0.644
SCP Inferior	44.26 $\pm$ 3.2	45.89 $\pm$ 3.7	<b>0.002</b>
SCP Nasal	44.91 $\pm$ 2.2	46.22 $\pm$ 3.2	<b>0.041</b>
<b>DCP Whole</b>	27.20 $\pm$ 6.7	26.33 $\pm$ 6.7	0.571
DCP Superior	45.31 $\pm$ 3.1	46.28 $\pm$ 3.0	0.100
DCP Temporal	48.36 $\pm$ 2.7	48.56 $\pm$ 3.2	0.448
DCP Inferior	46.99 $\pm$ 2.0	47.89 $\pm$ 2.1	<b>0.023</b>
DCP Nasal	48.81 $\pm$ 1.5	49.90 $\pm$ 2.2	<b>0.001</b>

OCTA: Optical coherence tomography angiography; SCP: Superficial capillary plexuse; DCP: Deep capillary plexuse; Mann-Whitney U test.

2). When comparing macular OCTA values, reduced VD was observed in the SCP whole, SCP inferior, SCP nasal, as well as in the DCP inferior and nasal quadrants, in acromegaly group (Table 3).

In the acromegaly group, ON was detected in 22 eyes (40.7%). In the patient group with ON, a negative correlation was found between RNFL superior thickness and RPC superior VD ( $r = -0.475$ ,  $p = 0.026$ ), while positive correlations were observed between RNFL temporal thickness and RPC temporal VD ( $r = 0.584$ ,  $p = 0.004$ ), as well as between RNFL nasal thickness and RPC nasal VD ( $r = 0.510$ ,  $p = 0.015$ ). In the patient group without ON, a negative correlation was found between RNFL nasal thickness and RPC nasal VD ( $r = -0.478$ ,  $p = 0.006$ ). In the acromegaly group, disease duration was negatively correlated with RNFL superior and temporal thickness ( $r = -0.343$ ,  $p = 0.011$  and  $r = -0.302$ ,  $p = 0.026$ , respectively). A negative correlation was also observed between the tumor diameter and SCP whole ( $r = -0.308$ ,  $p = 0.037$ ).

## DISCUSSION

PAs frequently cause visual disturbances due to their upward growth, which leads to compression of the optic chiasm. This pressure can result in visual function loss by affecting the retinal ganglion cells. Depending on the extent and severity of the compression, patients may experience decreased VA, constriction of the VF, and impaired color vision. Over the last two decades, the use of RNFL and GCC measurements, alongside VF testing, has become widespread in the follow-up of patients with PA.<sup>10,11</sup> The increasing use of OCTA has notably improved our ability to identify microvascular changes in optic neuropathies, with studies showing reduced RPC VD.<sup>12-14</sup> Similarly, OCTA researchs have expanded to investigate microvascular changes in PA.<sup>7,15-18</sup> Reduced VD at the RPC has been reported in cases of chiasmal compression and PA.<sup>16,17,19,20</sup> Our study corroborates these findings by demonstrating decreased VD in the inferior RPC quadrant in the acromegaly group.

Previous researchs have suggested strong correlations between RPC density, RNFL thickness. Dalorto et al. and Ben Ghezala et al. observed reduced peripapillary VD in cases of ON secondary to chiasmal tumors.<sup>17,21</sup> Notably, Ben Ghezala et al. found increased peripapillary VD in patients without ON, a finding that is particularly striking and highlights potential compensatory mechanisms. In our current study, we identified positive correlations between RNFL temporal thickness and RPC temporal VD, as well as between RNFL nasal thickness and RPC nasal VD in acromegaly patients with ON, highlighting the relationship between RNFL damage and VD. As is well known, chiasmal tumors tend to cause more pronounced damage in the nasal and temporal quadrants of the optic nerve. Therefore, the decreased VD in these quadrants could be secondary to the reduced metabolic demand caused by nerve loss. However, surprisingly, in patients with ON, a negative correlation was found between RNFL superior thickness and RPC superior VD, suggesting a potential compensatory mechanism in regions that are less impacted by tumor compression. This finding aligns with the compensatory mechanism proposed by Ben Ghezala et al. and Chen et al.<sup>19,21</sup> Likewise, in patients without

ON, the observed negative correlation between RNFL nasal thickness and RPC nasal VD reinforces the hypothesis of compensatory increases in VD prior to significant RNFL damage. As Suzuki et al. pointed out, while reductions in circumpapillary and macular VD could be associated with capillary loss or decreased metabolic demand, it cannot be definitively concluded that retinal VD damage happens only after RNFL and GCC loss or dysfunction.<sup>16</sup> Based on the literature and our study's findings, we suggest that a definitive positive correlation between RNFL thickness and peripapillary VD might not always be present. Microvascular compensatory changes could occur up to a certain stage, influenced by the extent of chiasmal compression. To thoroughly understand these microvascular changes, larger patient cohorts and longitudinal OCTA studies are essential.

As far as we know, only one study has reported peripapillary OCTA findings in patients with acromegaly. Karahan et al. observed reduced nasal RPC VD, consistent with our findings, and a negative correlation between IGF-1 levels and superior-nasal RPC VD, while our analysis found no such correlation.<sup>6</sup> Our study recorded a mean IGF-1 level of 415.39 ng/mL, which is notably higher than the 246.77 ng/mL reported by Karahan et al., although the duration of disease in our cohort was about half of that in their study.<sup>6</sup> Herrmann et al. demonstrated that increased disease duration correlates with coronary calcification, indicating changes in disease progression and endothelial dysfunction.<sup>22</sup> However, in our series, no significant correlation was found between disease duration and VD. While the presence of a tumoral mass is primarily responsible for microvascular alterations in acromegaly, it is important to note that other microvasculature changes, such as retinal capillary wall hypertrophy-known to occur in small vessels of other organs in acromegaly-may result from the combined effects of multiple factors, including disease duration, disease activity status, hormone status, the patient's metabolic condition, chronic oxidative damage, and inflammation. Therefore, IGF-1 levels alone cannot be solely blamed for these microvascular changes.

While previous studies have indicated a reduction in VD in the SCP or DCP in PA, Akdogan et al.

found no alteration in SCP in patients with prolactinoma compared to controls, but they reported increase in VD in various quadrants of the DCP.<sup>20,23</sup> Similarly, Wang et al. assessed patients with non-functional PA and detected no significant difference in SCP compared to controls, although an increase in VD at the DCP and an enlarged foveal avascular zone were observed.<sup>15</sup> Conversely, Lee et al. reported significant reductions in average and nasal SCP, as well as nasal DCP VD in patients with chiasmal compression.<sup>24</sup> Moreover, Dallorto et al. noted that superficial macular VD was significantly lower in PA patients with ON compared to healthy subjects.<sup>17</sup> Given these inconsistencies, it might be more appropriate to evaluate specific subgroups separately, considering factors such as whether the tumor is functional or non-functional, the type of hormone it secretes, or the presence of ON.

Although a few studies have assessed the retinal microvascular structure in acromegaly, their results have been varied. In the study by Selvinaz Erol et al., which involved patients with a longer disease duration and lower IGF-1 levels compared to our series, no difference in retinal OCTA values was found between acromegaly patients and healthy participants.<sup>25</sup> Karahan et al. noted that at the SCP segment, capillary density decreased only in the inferior parafoveal area in the acromegaly group, while at DCP, it decreased in all quadrants.<sup>18</sup> Likewise, Akay et al. demonstrated that there was a decrease in perfusion density in acromegaly.<sup>7</sup> In our current study, we observed decreased SCP whole, inferior, and nasal VD, as well as reduced DCP VD in the inferior and nasal quadrants in the acromegaly group. The literature findings also support the macular hypoperfusion which observed in our study.

In the study by Dallorto et al., no difference was observed in the macular OCTA analysis in the group without ON compared to the control group.<sup>17</sup> The increase in macular VDs before the development of VF defects has been reported in the literature, with the hypothesis that this might indicate a compensatory mechanism, while our results show a different finding.<sup>19</sup> In our study, the increase in SCP VD was found to be limited only to the superior quadrant ( $47.80\% \pm 3.1$  vs.  $46.06 \pm 3.2$ ,  $p=0.008$ ), in

that group. In the mentioned study, it was noted that the majority of the patients had non-functional PA, and the disease duration was approximately 1.5 years. Conversely, our study specifically focused on acromegaly patients, who had a longer disease duration. As is well-known, patients with acromegaly, due to high level of IGF-1, chronic endothelial damage, and various metabolic issues, are at an increased risk of developing retinopathy.<sup>26-28</sup> It is believed that the hormonal imbalance and its effects over time lead to increased endothelial damage, resulting in macular hypoperfusion even before the development of optic nerve damage. This hypothesis could be evaluated in future prospective studies where patients are regularly monitored over time.

The limitations of this study primarily include its retrospective design and heterogeneous patient population. Patients exhibited a range of characteristics, including the presence or absence of chiasmal compression or ON, active versus controlled disease, prior surgery or medication use. Nevertheless, our study is unique in showing that compensation observed in acromegaly patients without ON might persist even after the development of ON, particularly in the superior disc head, which has not been previously demonstrated.

## CONCLUSION

In conclusion, our study demonstrates retinal microvascular changes in acromegaly patients, marked by significantly decreased VD in the RPC inferior quadrant, as well as various quadrants in the macular SCP and DCP. The observed reduction in VD may be influenced by the long-term effects of GH and IGF-1, such as inflammation and endothelial dysfunction. Our findings suggest that vascular compensatory mechanisms may be activated earlier than the development of ON, and that compensation might continue in certain quadrants, even in the presence of ON. The noninvasive exploration of retinal microcirculation using OCTA may aid in understanding early microvascular changes in acromegaly patients and could offer a novel tool for assessing and monitoring treatment of mortality and morbidity risks, such as cardiovascular disease and retinopathy. Future researchs should focus on treat-

ment-naive patients without ON to better understand the effects of compensatory mechanisms and hormonal influences.

### Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

### Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise,

working conditions, share holding and similar situations in any firm.

### Authorship Contributions

**Idea/Concept:** Şerife Çiloğlu Hayat, Yusuf Cem Yılmaz, Merve Kelebek; **Design:** Şerife Çiloğlu Hayat, Yusuf Cem Yılmaz, Merve Kelebek; **Control/Supervision:** Şerife Çiloğlu Hayat, Yusuf Cem Yılmaz, Esra Hatipoğlu; **Data Collection and/or Processing:** Şerife Çiloğlu Hayat, Yusuf Cem Yılmaz; **Analysis and/or Interpretation:** Şerife Çiloğlu Hayat, Yusuf Cem Yılmaz; **Literature Review:** Şerife Çiloğlu Hayat, Yusuf Cem Yılmaz; **Writing the Article:** Şerife Çiloğlu Hayat, Yusuf Cem Yılmaz; **Critical Review:** Şerife Çiloğlu Hayat, Yusuf Cem Yılmaz; **References and Fundings:** Şerife Çiloğlu Hayat, Yusuf Cem Yılmaz, Esra Hatipoğlu; **Materials:** Şerife Çiloğlu Hayat, Yusuf Cem Yılmaz, Merve Kelebek, Esra Hatipoğlu.

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